Hypertension in Childhood

Treatment of Acute Nephritis with a Derivative of Veratrum Viride

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• **Alkavervir (Veriloid®), a new derivative of veratrum viride was used in the treatment of hypertension in ten children with acute nephritis. The patients had a variety of complications associated with hypertension—heart failure, convulsions, vomiting and headache. In all of them the blood pressure decreased soon after the drug was given.**

DURING THE winter and spring of 1952, 63 children with acute nephritis were observed on the wards of the Los Angeles Children's Hospital and the Los Angeles County General Hospital. Ten of them had signs and symptoms ordinarily associated with severe hypertension, and their blood pressure stabilized above 160 mm. of mercury systolic and 100 mm. diastolic. In an effort to lower these pressures and to relieve the associated hypertensive phenomena, the children were given a new derivative of an ancient drug. A prompt and uniform hypotensive effect was observed.

The Present Problems of Acute Nephritis

Since penicillin became available in adequate amounts many diseases associated with the beta streptococcus have been controlled more effectively and have been accompanied by fewer complications. A decreased incidence of these diseases in the general population has often coincided with this reduction in morbidity. This has held true for scarlet fever, streptococcal pharyngitis and erysipelas, and, to a lesser extent, for rheumatic fever. Acute nephritis appears to be an outstanding exception. Despite the use of antibiotics, the incidence of nephritis has shown little change in the past ten years. The number of cases seen each year at the Los Angeles Children's Hospital ranged between 20 and 35 for many years and has recently increased —to 42 in 1952 and to 57 in 1953. (This apparent epidemic coincides with a doubling of the overall admission rate to the hospital, and probably does not represent an absolute increase in the number of cases in the general population.)

Antibiotics also have had an important effect on other aspects of acute nephritis, notably the mortality rate. Upon investigation of autopsy records it was noted that the children who died with acute nephritis were, in most instances, overwhelmed by secondary infections and did not die of renal, heart, or lung complications of the disease. As antibiotics became generally available the death rate began to fall. Since 1947 there have been no deaths from acute nephritis at the Los Angeles Children's Hospital.

Therefore it might well be held that if antibiotics are given, and secondary infection controlled, the child will survive the disease regardless of the severity of nephritis. Yet one phase of the disease—the hypertensive—usually requires vigorous treatment. In this crucial period of acute nephritis the results of permitting the disease to run its course may well be heart failure, convulsions or coma. More remote possibilities are permanent cardiac or brain damage.

Acute Nephritis: Hypertensive Phase

The cause of hypertension associated with acute nephritis is not clear. Even less is understood, as a recent report by Derow[2] emphasized, about the relationship of hypertension and cardiac or cerebral phenomena. The clinical consequences of hypertension are known to a limited extent. Of major concern is the effect of sustained high blood pressure on the heart and brain. Therapy in the hypertensive phase is directed primarily toward prophylaxis of major cardiac and cerebral damage. Permanent renal damage is rare and treatment directed primarily toward the kidney usually is not indicated.

Myocarditis is a frequent concomitant of acute nephritis and it may occur in a normotensive patient. When hypertension is present the dangers of organic myocardial lesions, infarction and possibly permanent heart damage are increased. Similarly, it has been observed that the convulsions in encephalopathic states can occur when the blood pressure is normal. This suggests that factors other than hypertension may be present in most cases of brain disease associated with acute nephritis. But as the pressure rises quickly and steadily to excessively high levels the risk of coma and brain damage be-

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Submitted April 5, 1955.

comes proportionately greater. Notwithstanding the importance of other factors, it seems clear that acutely elevated blood pressure levels may have a harmful effect on the heart and brain of the sick child.

Hypotensive Agents

Specific therapy for the hypertensive phase is often difficult. Many agents have been tried but only a few have survived more than a few clinical trials. Surgical procedures, including kidney decapsulation and sympathectomy[1] have also been used. The many angles of approach to this problem suggest that the ideal agent has not yet been found.

An ideal hypotensive agent might be described as one which: (a) Reduces the blood pressure quickly and safely; (b) controls the factors other than hypertension, which contribute to cardiac failure, specifically factors which produce a low cardiac output; (c) reduces the dangers of damage to the brain by reversing cerebral vasospasm; (d) has a beneficial, or at least a nonharmful, effect on kidney function. The ideal agent should also have a wide margin of safety and a minimum of severe side effects, and it should be compatible with digitalis.

The one drug which has been used most frequently in this disease is magnesium sulfate. Despite its depressant effect on the central nervous system, and a similar depressant action on cardiac function, it has remained the agent of choice. Etteldorf and co-workers[3] noted that magnesium sulfate has a beneficial effect on the kidneys, increasing renal blood flow and renal output.[3] When used carefully magnesium sulfate does have this definite advantage over many other agents, particularly those which depress kidney function. The chief disadvantage of magnesium sulfate is its inconsistent action. In a high percentage of cases (in some series 50 per cent or more) magnesium sulfate has no appreciable hypotensive effect.

Veratrum Preparations

The agent used in the present series is a derivative of veratrum viride. In the past 2,000 years of medicine veratrum has been in and out of favor many times. It has always been considered an effective drug, but one whose effectiveness was matched or often overcome by its dangerous qualities. The nadir of its popularity was reached a few years ago when it was dropped from U.S.P. XII. In 1941 Goodman and Gilman[5] stated: "The drug is practically obsolete today, and enjoys a deserved oblivion."[5]

Recently, purified preparations of veratrum have been made available. One of these, alkavervir,* was selected for use in this study. This drug is an alkaloidal ester extract of veratrum, prepared by fractionation and standardized chemically and biologically. Data on alkavervir (Veriloid®) are summarized as follows:

1. *Hypotensive.* The hypotensive effect is achieved by generalized vasodilation, mediated through the central nervous system. The drug has neither a sympatholytic nor adrenergic blocking action. The patient is maintained in a state of circulatory equilibrium, but at a lowered arterial pressure.

2. *Cardiac.* Following Veriloid administration, Wilkins[7] noted an increase in cardiac output and bradycardia. The latter is not causally related to the hypotension but is vagal in origin, and can be abolished by vagotomy or by giving atropine. Electrocardiographic changes consist of reversal of the strain pattern during Veriloid-induced hypotension. In view of the fact that Kauntze and co-workers[6] used the drug in the therapy of congestive and hypertensive failure in adults, and it was given freely to patients already digitalized, it was anticipated that protective effect on the heart might be found—this in direct contrast to magnesium sulfate, which has a cardiac-depressant effect.

3. *Renal.* The renal bed shares in the generalized vasodilation which follows administration of the drug. This results in an initial decrease of renal blood flow, followed by a fairly rapid return to normal or above normal values. The urine output reflects this initial decrease; Goldman[4] observed that a smaller volume of urine is produced during the period of hemodynamic adjustment to the lower pressure.

MATERIALS AND METHODS

Veriloid may be administered by mouth, intramuscularly or intravenously. Inasmuch as the patients are usually nauseated and may be vomiting, and since close control over initial dosage is desirable, intravenous administration is usually preferred. In the present series the patients were observed for from 6 to 12 hours after admittance; during this time symptoms, behavior and evidences of encephalopathic conditions were recorded. Baseline blood pressure readings were made, an electrocardiogram obtained and blood drawn for nonprotein nitrogen determination. Indications for the use of hypotensive agents were considered to be systolic pressure of 160 mm. of mercury and/or diastolic pressure of 100 mm. or more; or lower blood pressure levels if there was evidence of heart failure or cerebral symptoms.

The following regimen is suggested:

Dosage: Veriloid administration (intravenously)

*Veriloid,® NNR, Riker Laboratory, Los Angeles.

consists of two phases, an initial rapid infusion followed by slow intravenous drip. Initially: 0.022 cc. of Veriloid solution per kilogram of body weight over a period of 20 minutes. This amount is diluted to a volume of 10 cc. with 5 per cent glucose solution. (For example, if the patient weighs 20 kg. then the initial dose is 0.022 cc. × 20 = 0.44 cc. of Veriloid, diluted to 10 cc. in a 5 per cent glucose solution.)

(a) The injection should be made at the rate of 0.5 cc. of this diluted solution per minute for eight minutes (total of 4 cc.) with continuous observation of blood pressure.

(b) Wait two minutes.

(c) Continue at the rate of 0.5 cc. per minute for six more minutes, watching blood pressure closely. (The total given thus far is 7 cc.)

(d) Wait two minutes.

(e) Continue at the rate of 0.5 cc. per minute for six more minutes, watching blood pressure closely. This will exhaust the supply in the syringe. (Total 10 cc.) If, after a 15-minute interval, the blood pressure is not lowered to the desired level, repeat whatever part of a similar 10 cc. preparation is required to bring the blood pressure to the level desired. Always stop when a 20 mm. fall is observed, and wait until the blood pressure levels off before continuing.

Maintenance: Start slow intravenous infusion using 5 per cent or 10 per cent glucose as the diluent. Give 0.13 cc. Veriloid per kilogram of body weight, in total solution of 22 cc. per kilogram of body weight. Infuse at rate of 5 drops per 10 kg. of body weight per minute. (For example, with a 20 kg. patient, 0.13 cc. of Veriloid × 20 = 2.6 cc. of Veriloid to be added to 20 × 22 cc. = 440 cc. of a 5 per cent glucose solution given at rate of 2 × 5 drops = 10 drops per minute.)

Blood pressure must be taken and recorded every 15 minutes while the maintenance infusion is running. It may be set up to run 15 to 20 hours if necessary.

Further medication with Veriloid should be determined on the basis of subsequent episodes of hypertension. After the initial infusion and maintenance dosage the patient may "escape" from the effects of the drug, and the blood pressure climb to near the initial levels. A second maintenance infusion may then be used.

Overdosage results in extreme hypotension with eventual collapse, bradycardia and cardiac irregularities. These complications are rare, but to relieve them there must be at the bedside of each patient receiving the drug:

1. One ampule of ephedrine sulfate 2½ per cent. Give 1 cc. (25 mg.) intramuscularly.

2. Atropine sulfate 1:1000. Give 0.43 mg. intramuscularly to overcome bradycardia.

RESULTS

Using the criteria and methods as outlined above, ten children were given Veriloid. A prompt hypotensive effect was observed, and a characteristic general pattern of response to Veriloid was noted in each instance.

It was found that the blood pressure could be reduced to a selected level, or to normal or subnormal levels, by changing the rate of the infusion. No attempt was made to produce normal or hypotensive levels, since a fall of only 20 or 30 mg. was often sufficient to relieve encephalopathic states and to reduce the hypertensive strain on the patient.

Three typical case histories follow:

CASE 1. A 12-year-old Mexican boy entered the hospital in a semicomatose condition. Three weeks before, he had apparently made uneventful recovery from scarlet fever, although he occasionally complained of persistent headache. Forty-eight hours before admission he began to vomit, and on the morning of entry had a convulsion. Intermittent convulsions lasted eight hours and were accompanied by cyanosis. Initial physical examination showed a disoriented, combative boy with moderate, generalized edema and blood pressure of 180/130 mm. of mercury. The heart was enlarged to percussion and on roentgen examination a widened cardiac shadow was seen. An electrocardiogram was within normal limits. The urine was grossly bloody, contained red blood cell casts, and gave a strongly positive reaction for albumin. The nonprotein nitrogen content of the blood was 113 mg. per 100 cc. During the first four hours on the ward the patient remained semiconscious and belligerent, and had periodic convulsions of a tonic-clonic pattern. Blood pressure stabilized at 170/120 mm. of mercury. At this time Veriloid was given intravenously, and 20 minutes later the patient became responsive and cooperative. The blood pressure was 140/100 mm. Two hours later the patient fell asleep, and the blood pressure at that time was 120/90 mm. During maintenance Veriloid therapy that was continued over a period of 12 hours, the blood pressure stabilized at 130/90 mm. of mercury. The following day the nonprotein nitrogen was 54 mg. per 100 cc. and the patient began to lose weight. Recovery was without incident, and two years after the illness, urinary findings and blood pressure were normal.

CASE 2. A 7-year-old Mexican boy entered the hospital with signs of acute cardiac failure. Two weeks before entry he had had an attack of acute pharyngitis, followed one week later by swelling of the face, abdomen and scrotum. Thirty-six hours before entry he became dyspneic, 12 hours later was orthopneic, and on the morning of admission was cyanotic. Upon initial examination, deep cyanosis,

generalized edema and orthopnea were noted. The blood pressure was 160/120 mm. of mercury. The patient seemed acutely uncomfortable. The heart was enlarged to percussion, and the heart rate ranged from 160 to 180. Conditions observed upon roentgen examination of the chest were consistent with pulmonary congestion. The electrocardiogram was grossly abnormal. Albumin, red blood cells and red blood casts were noted in the urine. The nonprotein nitrogen content of the blood was 58 mg. per 100 cc.

Upon entry the patient was given digitalis and after six hours, during which time the blood pressure stabilized at 155/120 mm. of mercury, Veriloid was started intravenously. There was a rapid fall in blood pressure with leveling off at 100/80 mm. After nine hours Veriloid was discontinued. During the next four days edema subsided. No restrictions on fluid, sodium or diet were imposed during this period. The heart returned to normal size and recovery was uneventful.

CASE 3. A 4-year-old girl entered the hospital because of generalized edema. Two weeks before admission the child had received penicillin for a mild sore throat. Subsequently she had been well until four days before entry, when abdominal swelling was observed. Two days later severe shortness of breath developed. On initial examination the child seemed acutely ill and dyspneic. Blood pressure stabilized at 150/120 mm. of mercury during six hours of observation. There was abdominal distention with evidence that pressure on the diaphragm from below was compressing the chest. Films of the heart showed an enlarged cardiac silhouette and vascular shadows consistent with pulmonary engorgement. Gross hematuria was noted, and red blood cell casts were observed on microscopic examination of the urinary sediment. Nonprotein nitrogen was 52 mg. per 100 cc. of blood. Veriloid administration was followed by a prompt drop of the blood pressure to 115/90 mm. of mercury. During the next eight hours the patient seemed more comfortable and the chest cleared. Grossly abnormal urinary findings were observed for a period of ten days. Recovery thereafter was without incident.

DISCUSSION

It is not reasonable to assume that Veriloid or any other hypotensive agent now available effects more than a temporary reversal of hypertension. The blood pressure will again rise to high levels shortly after the drug is discontinued. But meanwhile a temporary reversal has been obtained, and this may be all that is needed. Furthermore, it should not be assumed that because a drug worked well and uniformly in ten children it constitutes an ideal agent. The variability of blood pressure both in health and disease is such that one cannot always be sure that the drug that is given and the blood pressure readings that follow are necessarily cause and effect. At present, from this limited series it seems reasonable to conclude only this: Veriloid deserves further clinical trial in the hypertensive phase of acute nephritis in childhood.

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